Tetrahedron Letters 49 (2008) 5258–5261

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Heteroaromatic alanine derivatives bearing (oligo)thiophene units: synthesis and photophysical properties

Susana P. G. Costa [a,*], Elisabete Oliveira [b], Carlos Lodeiro [b,*], M. Manuela M. Raposo [a]

[a] Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[b] REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Monte de Caparica, Portugal

ARTICLE INFO

Article history:
Received 30 May 2008
Revised 19 June 2008
Accepted 24 June 2008
Available online 28 June 2008

Keywords:
Amino acids
(Oligo)thiophene
Benzoxazole
Alanine
Fluorophores
Fluorescent markers

ABSTRACT

A series of new benzoxazolylalanine derivatives bearing (oligo)thiophene units at the side chain were synthesized in good yields. The photophysical characterization of these amino acids was performed by UV–vis absorption and fluorescence emission studies and revealed that some of the compounds display high fluorescent quantum yields, making them good candidates for application as fluorescent probes.

The insertion of coded and unnatural amino acids into the backbone of both natural and synthetic polymers is a very appealing area of research since it can lead to the development of macromolecules possessing biomimetic characteristics, with unique structural and biological properties. By synthetic manipulation at the side chain of the coded amino acids, new functions and functional relationships can be generated as well as altered physicochemical properties, such as luminescence, conducting ability, higher thermal stability and metal ion and other analytes recognition ability, amongst other properties. Furthermore, the chirality of the amino acid should make these polymers suitable for chiral recognition and induce chain helicity in aggregated phases.[1] The fact that amino acids and peptides are known to bind a variety of metal ions as they contain a large number of potential donor atoms through the peptide backbone and amino acid side chains has encouraged their application to the solution-based detection of metals[2] and as solid-state metal-ion biosensors.[3]

2-Benzoxazole derivatives have long been recognized as very interesting biologically active compounds as they display high lipophilicity and broad range biological activity. In recent reports, several derivatives have been presented as antifungal, antimicrobial and anticancer agents.[4] Moreover, benzoxazoles also have excellent optical properties (broad spectral windows, high molar absorption coefficients and fluorescence quantum yields) and they have been described as fluorescent probes and sensing materials, namely as fluorescent and/or colorimetric sensors for metals, anionic species and pharmaceutical analysis.[2c,5] Thiophene and its derivatives also display interesting biological activity and important electroluminescent properties with wide applications in polymer science, which has prompted their application as energy transfer and light-harvesting systems, for optical and electronic devices,[6] as sensors and as fluorescent markers.[7] Furthermore, the combination of amino acid building blocks and thiophene derivatives has resulted in several examples of heteroaromatic amino acids with application as ligands of the NMDA receptor, monomers for conducting polymers with complexing ability, paramagnetic amino acids for probing protein dynamics, as UV- and pharmaceutically active amino acids for incorporation into mutant proteins with changed optical and thermodynamic properties.[8]

The importance of the several abovementioned applications of thiophene, benzoxazole and amino acid derivatives reveals that there is a practical interest on the synthesis of new and more complex systems that combine these units. Therefore, in order to contribute and expand the body of work published in this area in the last years, we decided to design new amino acid-based systems consisting of functionalized alanines containing these heterocyclic nuclei. The (oligo)thienyl-benzoxazole amino acid derivatives, because of the presence of amino and carboxyl groups, can be incorporated into peptide chains and as such used as an energy donor in conformational studies of peptides by means of fluorescence or be used as fluorescence markers.

---

* Corresponding authors. Tel.: +351 253 604054; fax: +351 253 604382 (S.P.G.C.).
E-mail address: spc@quimica.uminho.pt (S. P. G. Costa).

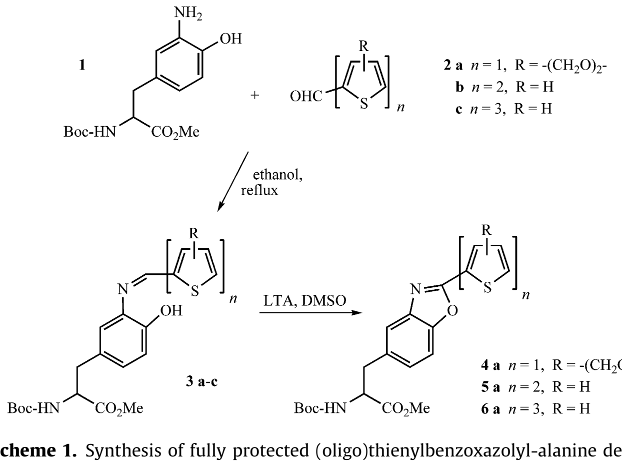
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.109

Following our previous research in the synthesis and characterization of unnatural amino acids,[9] benz-X-azole derivatives with interesting optical properties[10] and heterocyclic colorimetric/fluorescent chemosensors containing (oligo)thiophene, benzoxazole and amino acid moieties,[2c,11] we now report the synthesis and characterization of a series of benzoxazolyl alanine derivatives bearing (oligo)thiophene units at the side chain. With the study of these new (oligo)thienyl-benzoxazolyl-alanines we intend to evaluate the effect of the length of the (oligo)thienyl group at the position 2 of the benzoxazole moiety in the photophysical properties of the resulting compounds.

The new(oligo)thienyl-benzoxazolyl-alanines **4–6** with ethylenedioxythiophene, bithiophene and terthiophene units linked to the benzoxazolyl alanine system were synthesized in good yields, by a multistep synthesis, in order to compare the photophysical properties of compounds **4–6** with our recently reported system with thiophene.[2c] Several (oligo)thiophene moieties were used in order to study the influence of the structure modification (e.g., the rigidification of the thiophene derivative by adding a ethylenedioxy bridge in compound **4a** and increase of the π-conjugated system in compounds **5a** and **6a**) on the overall optical properties of compounds **4–6**.

Starting from commercially available 3-nitro-L-tyrosine, *N*-Boc-3-amino-L-tyrosine methyl ester **1** was obtained by using simple synthetic procedures.[2c] The synthesis of 2-formyl-(oligo)thiophenes **2a**[12] and **2c**[13] has been previously reported by us. Condensation of compounds **1** and **2a–c** in ethanol afforded the corresponding imino derivatives **3a–c**, as stable solids which allowed their characterization. By reaction with lead tetraacetate (LTA) in DMSO, the imino compounds were oxidized to the [2-(oligothienyl)benzoxazol-5-yl] alanine derivatives **4a–6a**, in 56–74% yield (Scheme 1, Table 1).[14]

In order to study the effect of the N- and C-terminal protecting group of these amino acids in the photophysical properties, compound **4a** was then selectively deprotected at its C- and N-terminus, yielding the corresponding *N*-Boc protected compound **4b**[15] and the fully deprotected ethylenodioxythienyl-benzoxazolyl-alanine derivative **4c**.[16] By a similar procedure, compounds **5a–6a** were selectively deprotected, resulting in the corresponding *N*-Boc protected **5b–6b** and the fully deprotected alanine derivatives **5c–6c** (Scheme 2, Table 1). The structures of the new (oligo)thienyl-benzoxazolyl-alanines **4–6** were unambiguously confirmed by their analytical and spectral data.

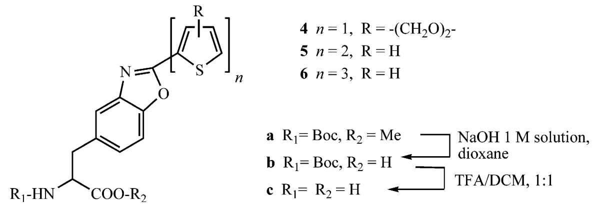


Scheme 1. Synthesis of fully protected (oligo)thienylbenzoxazolyl-alanine derivatives **4a–6a**.

Table 1
Yields, UV–vis absorption and emission data for (oligo)thienylbenzoxazolyl-alanines **4–6** in absolute ethanol

Entry	Compd.	Yield (%)	Absorption λ_{max} (nm) (logε)	Emission λ_{max} (nm)	Stokes' shift (nm)	Quantum yield Φ_F
1	**4a**	56	314 (4.37)	398	84	0.03
2	**4b**	84	320 (4.12)	400	80	0.03
3	**4c**	54	320 (4.28)	386	66	0.05
4	**5a**	74	365 (4.32)	445	80	0.46
5	**5b**	95	365 (4.39)	442	77	0.37
6	**5c**	55	365 (4.29)	448	83	0.55
7	**6a**	72	400 (4.57)	490	90	0.10
8	**6b**	96	400 (4.49)	480	80	0.13
9	**6c**	60	—[a]	—[a]	—[a]	—[a]

[a] The evaluation of the photophysical properties of compound **6c** was not possible due to insolubility.



Scheme 2. Synthesis of *N*- and *C*-terminal deprotected (oligo)thienylbenzoxazolyl-alanine derivatives **4a–c** to **6a–c**.

The absorption and emission spectra of (oligo)thienylbenzoxazolyl-alanines **4–6** were measured in absolute ethanol (1–2 × 10^{-5} M solution) (Table 1). The nature of the thiophenic substituent at position 2 of the benzoxazole had a clear influence on the absorption and emission bands of compounds **4–6**. The wavelength of maximum absorption was shifted to longer wavelengths as the number of thiophene units increased, ca. 50 nm for each added thiophene (Table 1, entries 1, 4 and 7). The same trend was observed in the emission spectra as the position of the wavelength of maximum emission was red-shifted with the increase of the number of thiophene units, which varied from λ_{em} = 398 nm for **4a** to λ_{em} = 490 nm for **6a** (Fig. 1).

The fluorescence quantum yields were determined using a 0.1 M solution of 1-naphthylamine in cyclohexane as standard (Φ_F = 0.46)[17] and (oligo)thienylbenzoxazolyl-alanines **4–6** exhibited good to excellent relative fluorescence quantum yields. Alanines **5a–c**, with a bithiophene at position 2 of the benzoxazole, were found to be strongly emissive (0.37 < Φ_F < 0.55) while compounds **6a–c**, with a terthiophene substituent, displayed much lower quantum yields (0.10 < Φ_F < 0.13). The ethylenedioxythienylbenzoxazolyl-alanines **4a–c** displayed residual fluorescence (Table 1, entries 1–3). For this compound it was found that the rigidity introduced by the ethylenedioxy bridge on the thiophene ring had practically no effect on the wavelengths of maximum absorption and emission, although a strongly deleterious effect

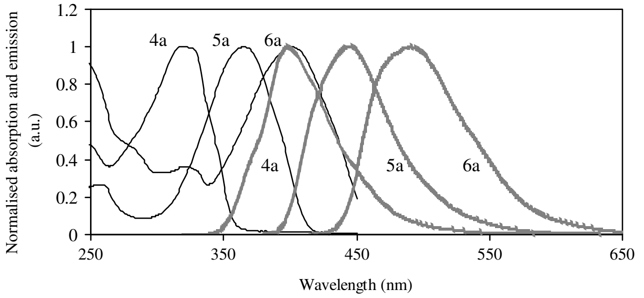


Figure 1. Normalized UV–vis absorption and emission spectra of compounds **4a**, **5a** and **6a** in absolute ethanol at *T* = 298 K (**4a**, λ_{exc} = 314 nm; **5a**, λ_{exc} = 365 nm; **6a**, λ_{exc} = 400 nm) (absorption, full line; emission, dotted line).

on the fluorescence quantum yield was observed, when compared to 2-thienylbenzoxazolyl-alanine which was reported to have a fluorescence quantum yield of 0.80.[2c] A related alanine derivative containing a benzoxazole bearing a methylthiophene was reported by other authors,[18] with the wavelength of maximum emission at 354 nm and a relative fluorescence quantum yield of 0.64.

The fluorescence quantum yield of nonsubstituted (oligo)thiophenes is expected to increase as the oligothiophene chain length increases, due to a further extension of the conjugated π-system. On the other hand, the heavy atom induced spin–orbit coupling by the sulfur atoms can give rise to a very efficient intersystem crossing mechanism, thus lowering the emission.[19] Moreover, azomethine nitrogens contribute to the heavy atom effect concomitant with the increased degree of conjugation.[19c] Also, the different chains (thiophene, bithiophene and terthiophene) should exhibit different degrees of torsion between the thiophene units, which leads to variations in the effectivity conjugation length, affecting the planarity of the whole heteroaromatic system.[19d] In our case, we believe that a combination of the abovementioned effects could be responsible for the trend observed in our results.

Keeping in mind further applications of these amino acids as emissive probes for energy transfer or FRET (Fluorescence Resonance Energy Transfer) studies in more complex structures as peptides chains, in Figure 1 can also be seen the good superposition of some absorption and emission spectra (e.g., compounds **6a** and **4a**), which opens up a very wide range of potential interesting applications to be explored.

As can be seen by the results, the presence of C- and N-terminal protecting groups does not affect the position of the absorption and emission bands, nor the fluorescence quantum yield, which does not vary significantly, within the same series of compounds (e.g., compare entries 1–3 in Table 1). In order to assess the influence of the solvent polarity in the photophysical properties of alanines **4**–**6**, spectra were run in cyclohexane, dioxane, acetonitrile and ethanol/water (1:1) and the obtained results showed that no solvatochromic effect was observed, suggesting that these compounds are solvent polarity independent.

In summary, we have achieved the synthesis of new fluorescent heteroaromatic amino acid derivatives **4**–**6** containing (oligo)thiophene and benzoxazole moieties combined with an alanine residue by simple procedures in good yields and their photophysical properties were evaluated. Due to their interesting photophysical properties these heterocyclic alanine derivatives could find application as useful building blocks for peptide-based fluorimetric chemosensors, as fluorescent markers and probes for FRET studies in peptides. Studies on the application of these new derivatives as chemosensors are currently ongoing and it is expected that their metal ion sensing ability can be comparable to that of 2-thienylbenzoxazolylalanine, which has been found to respond via a fluorescence quenching effect to the presence of Cu(II), Ni(II) and Hg(II) in a very efficient manner.[2c]

Acknowledgements

Thanks are due to *Fundação para a Ciência e Tecnologia* (Portugal) for financial support through project PTDC/QUI/66250/2006 and a Ph.D. grant to E.O. (SFRH/BD/35905/2007).

Supplementary data

Characterization data (^{1}H and ^{13}C NMR, MS and HRMS and UV–vis) for derivatives **4a**–**c** and **6a**–**c** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.109.

References and notes

1. (a) Nilsson, K. P. R.; Andersson, M. R.; Inganäs, O. *J. Phys.: Condens. Matter* **2002**, *14*, 10011–10020; (b) Mucci, A.; Parenti, F.; Schenetti, L. *Macromol. Rapid Commun.* **2003**, *24*, 547–550.
2. (a) Zheng, Y.; Gattás-Asfura, K. M.; Konka, V.; Leblanc, R. M. *Chem. Commun.* **2002**, 2350–2351; (b) Zheng, Y.; Cao, X.; Orbulescu, J.; Konka, V.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *Anal. Chem.* **2003**, *75*, 1706–1712; (c) Costa, S. P. G.; Oliveira, E.; Lodeiro, C.; Raposo, M. M. M. *Sensors* **2007**, *7*, 2096–2114.
3. (a) Gooding, J. J.; Hibbert, D. B.; Yang, W. *Sensors* **2001**, *1*, 75–90; (b) Yang, W.; Gooding, J. J.; Hibbert, D. B. *J. Electroanal. Chem.* **2001**, *516*, 10–16.
4. (a) Vinsova, J.; Cermakova, K.; Tomeckova, A.; Ceckova, M.; Jampilek, J.; Cermak, P.; Kunes, J.; Dolezal, M.; Staud, F. *Bioorg. Med. Chem.* **2006**, *14*, 5850–5865; (b) Jauhari, P. K.; Bhavani, A.; Varalwar, S.; Singhal, K.; Raj, P. *Med. Chem. Res.*, in press.; (c) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775–1783.
5. (a) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2003**, *126*, 712–713; (b) Shamsipur, M.; Poursaberi, T.; Karami, A. R.; Hosseini, M.; Momeni, A.; Alizadeh, N.; Yousefi, M.; Ganjali, M. R. *Anal. Chim. Acta* **2004**, *501*, 55–60; (c) Milewska, M.; Skwierawska, A.; Guzow, K.; Szmigiel, D.; Wiczk, W. *Inorg. Chem. Commun.* **2005**, *8*, 947–950; (d) Zang, X.-B.; Peng, J.; He, C.-L.; Shen, G.-L.; Yu, R.-Q. *Anal. Chim. Acta* **2006**, *567*, 189–195.
6. (a) Roncali, J. *Chem. Rev.* **1997**, *97*, 173–206; (b) Steybe, F.; Effenberger, F.; Beckman, S.; Gluber, U.; Bosshard, C.; Gunter, P. *Tetrahedron* **1998**, *54*, 8469–8480; (c) Van Mullekom, H. A. M.; Vekemans, J. A. J. M.; Havinga, E. E.; Meijer, E. W. *Mater. Sci. Eng.* **2001**, *32*, 1–40.
7. (a) Yu, J.; Shirota, Y. *Chem. Lett.* **2002**, *31*, 984–985; (b) Lin, S.-C.; Sun, S.-S. *Chem. Mater.* **2002**, *14*, 1884–1890; (c) Destri, S.; Pasini, M.; Botta, C.; Porzio, W.; Bertini, F.; Marchio, L. *J. Mater. Chem.* **2002**, *12*, 924; (d) Béra-Abérem, M.; Ho, H.-A.; Leclerc, M. *Tetrahedron* **2004**, *60*, 11169–11173; (e) Barbarella, G.; Melucci, M.; Sotgiu, G. *Adv. Mater.* **2005**, *17*, 1581–1593.
8. (a) Budisa, N.; Alefelder, S.; Bae, J. H.; Golbik, R.; Minks, C.; Huber, R.; Moroder, L. *Protein Sci.* **2001**, *10*, 1281–1292; (b) Lima, P. G.; Caruso, R. R. B.; Alves, S. O.; Pessoa, R. F.; Mendonça-Silva, D. L.; Nunes, R. J.; Noël, F.; Castro, N. G.; Costa, P. R. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4399–4403; (c) Brembilla, A.; Collard, A.; Henry, B.; Jadamiec, M.; Lapkowski, M.; Matlengiewicz, M.; Rodehüser, L. *Phosphorus, Sulfur and Silicon* **2007**, *182*, 723–734; (d) Kálai, T.; Schindler, J.; Balog, M.; Fogassy, E.; Hideg, K. *Tetrahedron* **2008**, *64*, 1094–1100.
9. (a) Costa, S. P. G.; Maia, H. L. S.; Pereira-Lima, S. M. M. A. *Org. Biomol. Chem.* **2003**, *1*, 1475–1479; (b) Jiang, W.-Q.; Costa, S. P. G.; Maia, H. L. S. *Org. Biomol. Chem.* **2003**, *1*, 3804–3810.
10. (a) Batista, R. M. F.; Costa, S. P. G.; Raposo, M. M. M. *Tetrahedron Lett.* **2004**, *45*, 2825–2828; (b) Costa, S. P. G.; Batista, R. M. F.; Sousa, A. M. R. C.; Raposo, M. M. M. *Mater. Sci. Forum* **2006**, *514–516*, 147–151; (c) Costa, S. P. G.; Batista, R. M. F.; Cardoso, P.; Belsey, M.; Raposo, M. M. M. *Eur. J. Org. Chem.* **2006**, *17*, 3938–3946; (d) Batista, R. M. F.; Costa, S. P. G.; Malheiro, E. L.; Belsey, M.; Raposo, M. M. M. *Tetrahedron* **2007**, *63*, 4258–4265; (e) Batista, R. M. F.; Costa, S. P. G.; Belsley, M.; Raposo, M. M. M. *Tetrahedron* **2007**, *63*, 9842–9849; (f) Pina, J.; Seixas de Melo, J.; Burrows, H. D.; Batista, R. M. F.; Costa, S. P. G.; Raposo, M. M. M. *J. Phys. Chem. A* **2007**, *111*, 8574–8578.
11. Batista, R. M. F.; Oliveira, E.; Costa, S. P. G.; Lodeiro, C.; Raposo, M. M. M. *Org. Lett.* **2007**, *9*, 3201–3204.
12. Costa, F.; Silva, C. J. R.; Raposo, M. M. M.; Fonseca, A. M.; Neves, I. C.; Carvalho, A. P.; Pires, J. *Micropor. Mesopor. Mater.* **2004**, *72*, 111–118.
13. Batista, R. M. F.; Costa, S. P. G.; Belsley, M.; Lodeiro, C.; Raposo, M. M. M. *Tetrahedron*, in press.
14. General procedure for the synthesis of alanines **4a**–**6a**: compound **1** (1 equiv) was stirred with the corresponding 2-formyl (oligo)thiophene **2** (1 equiv) and heated in ethanol at reflux (5 mL/equiv) for 3 h. The solvent was evaporated and the crude imine **3** used in the next step without further purification.
    N-tert-Butyloxycarbonyl 3-(bithien-2′-yl)imino-L-tyrosine methyl ester **3b** (crude): yellow solid. Mp 162.5–163.6 °C. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 2.96–3.12 (m, 2H, β CH_2), 3.73 (s, 3H, CH_3), 4.52–4.60 (m, 1H, α-H), 5.01 (d, J = 7.8 Hz, 1H, NH), 6.92–6.95 (m, 2H, H-2 + H-5), 7.06–7.10 (m, 2H, H-6 + H-4″), 7.22 (d, J = 4.2 Hz, 1H, H-3′), 7.31–7.34 (m, 2H, H-3″ + H-5″), 7.41 (d, J = 3.9 Hz, 1H, H-4′), 8.70 (s, 1H, N=CH) ppm. ^{13}C NMR ($CDCl_3$) δ 28.31 ($C(\mathit{CH}_3)_3$), 37.90 (β CH_2), 52.26 (CH_3), 54.46 (αC), 80.01 ($\mathit{C}(CH_3)_3$), 115.03 (C2), 116.45 (C6), 124.18 (C3′), 125.18 (C3″), 126.02 (C5″), 127.61 (C1), 128.21 (C4″), 129.49 (C5), 133.51 (C4′), 134.95 (C3), 136.86 (C2′ or C2″), 141.09 (C5′), 142.88 (C2′ or C2″), 149.37 (N=CH), 151.25 (C4), 155.12 (C=O Boc), 172.46 (C=O ester) ppm. MS (FAB) *m/z* (%): 487 ($[M+H]^+$, 63), 486 (28), 431 (26), 307 (38), 298 (36), 155 (30), 154 (100). HRMS: (FAB) *m/z* for $C_{24}H_{27}N_2O_5S_2$; calcd 487.1361, found 487.1368. Calcd for $C_{24}H_{26}N_2O_5S_2$: C, 59.24; H, 5.39; N, 5.76; S, 13.18. Found: C, 59.41; H, 5.48; N, 5.76; S, 13.23.
    The corresponding crude imine **3** (1 equiv) and lead tetraacetate (1.5 equiv) were stirred at room temperature in DMSO (5 mL/equiv) for 3 days. The mixture was poured over water and extracted with ethyl acetate (3 × 10 mL). After drying with anhydrous magnesium sulfate and evaporation of the solvent under reduced pressure, the crude compound was submitted to column chromatography with silica gel by elution with dichloromethane.
    N-tert-Butyloxycarbonyl [2-(bithien-2′-yl)benzoxazol-5-yl]-L-alanine methyl ester **5a**: yellow solid (0.198 g, 74%). Mp 107.0–108.7 °C. UV (ethanol): λ_{max} nm (log ε) 365.0 (4.53). ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H, $C(CH_3)_3$), 3.16–3.29 (m, 2H, β CH_2), 3.74 (s, 3H, CH_3), 4.63–4.66 (m, 1H, α-H), 5.03 (d, J = 8.1 Hz, 1H, NH), 7.06–7.09 (m, 1H, H-4″), 7.11 (dd, J = 1.2 and 8.4 Hz, 1H, H-6), 7.24 (d,

J = 4.2 Hz, 1H, H-4′), 7.31–7.34 (m, 2H, H-7 and H-3″ or 5″), 7.44–7.46 (m, 1H, H-3″ or 5″), 7.48 (s, 1H, H-4), 7.80 (d, *J* = 4.2 Hz, 1H, H-3′) ppm. ^{13}C NMR ($CDCl_3$) δ 28.24 ($C(CH_3)_3$), 38.26 (β CH_2), 52.29 (CH_3), 54.57 (αC), 79.99 ($\mathit{C}(CH_3)_3$), 110.20 (C7), 120.23 (C4), 124.43 (C4′), 125.07 (C5″), 125.90 (C3″), 126.31 (C6), 127.38 (C2′), 128.14 (C4″), 130.66 (C3′), 132.85 (C5), 136.19 (C2″), 142.30 (C5′), 142.35 (C3a), 149.62 (C7a), 155.05 (C=O Boc), 159.01 (C2), 172.08 (C=O ester) ppm. MS (FAB) *m/z* (%): 486 ($[M+2H]^+$, 34), 485 ($[M+H]^+$, 87), 430 (32), 429 (100), 325 (37), 297 (38), 296 (31), 293 (58), 193 (28), 185 (71), 171 (34). HRMS: (FAB) *m/z* for $C_{24}H_{25}N_2O_5S_2$; calcd 485.1205, found 485.1212.

15. General procedure for the synthesis of alanines **4b**–**6b**: the corresponding alanine methyl ester (1 equiv) was dissolved in 1,4-dioxane (1 mL/equiv), in an ice bath and sodium hydroxide 1 M aqueous solution (1.5 equiv) was added dropwise. The mixture was stirred at room temperature for 3 h. The pH was adjusted to 2–3 by addition of $KHSO_4$ 1 M aqueous solution and extracted with ethyl acetate (3 × 10 mL). After drying with anhydrous magnesium sulfate and evaporation of the solvent, the residue was triturated with diethyl ether and the pure compound was obtained as a solid.
    N-*tert*-Butyloxycarbonyl [2-(bithien-2′-yl)benzoxazol-5-yl]-L-alanine **5b**: yellow solid (0.064 g, 95%). Mp 183.5–185.0 °C. UV (ethanol): λ_{max} nm (log ε) 365.0 (4.53). ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H, $C(CH_3)_3$), 3.34 (d, *J* = 4.5 Hz, 2H, β CH_2), 4.65–4.72 (m, 1H, α-H), 5.15 (d, *J* = 7.5 Hz, 1H, NH), 7.05–7.08 (m, 1H, H-4″), 7.18–7.22 (m, 2H, H-6 + H-4′), 7.29–7.33 (m, 2H, H-3″ + H-5″), 7.47 (d, *J* = 8.4 Hz, 1H, H-7), 7.61 (d, *J* = 1.2 Hz, 1H, H-4), 7.81 (d, *J* = 3.9 Hz, 1H, H-3′) ppm. ^{13}C NMR ($CDCl_3$) δ 28.30 ($C(CH_3)_3$), 37.96 (β CH_2), 54.50 (αC), 80.10 ($\mathit{C}(CH_3)_3$), 110.22 (C7), 120.18 (C4), 124.47 (C4′), 125.13 (C5″), 125.79 (C3″), 126.58 (C6), 127.35 (C2′), 128.25 (C4″), 130.43 (C3′), 133.01 (C5), 136.10 (C2″), 142.20 (C5′), 142.03 (C3a), 149.42 (C7a), 155.05 (C=O Boc), 159.01 (C2), 174.65 (CO_2H) ppm. MS (FAB) *m/z* (%): 472 ($[M+2H]^+$, 6), 471 ($[M+H]^+$, 18), 470 (M^+, 10), 415 (11), 307 (32), 289 (16), 166 (11), 155 (30), 154 (100). HRMS: (FAB) *m/z* for $C_{23}H_{23}N_2O_5S_2$; calcd 471.1048, found 471.1054.
16. General procedure for the synthesis of alanines **4c**–**6c**: the corresponding *N*-Boc protected alanine was stirred in a trifluoroacetic acid/dichloromethane solution (1:1, 4 mL/mmol) at room temperature for 2 h. The solvent was evaporated, the solid residue dissolved in pH 8 aqueous buffer solution and extracted with ethyl acetate (3 × 10 mL). After drying with anhydrous magnesium sulfate and evaporation of the solvent, the product was isolated as a solid.
    [2-(Bithien-2′-yl)benzoxazol-5-yl]-L-alanine **5c**: light yellow solid (0.031 g, 55%). Mp 248.6–250.2 °C. UV (ethanol): λ_{max} nm (log ε) 365.0 (4.04). ^1H NMR (DMSO-d_6) δ 3.05–3.15 (m, 2H, β CH_2), 4.10–4.17 (m, 1H, α-H), 7.15–7.19 (m, 1H, H-4″), 7.30 (dd, *J* = 1.2 and 8.4 Hz, 1H, H-6), 7.48 (d, *J* = 3.9 Hz, 1H, H-4′), 7.54 (dd, *J* = 1.2 and 3.6 Hz, 1H, H-3″ or H-5″), 7.65 (d, *J* = 1.2 Hz, 1H, H-4), 7.66 (dd, *J* = 1.8 and 5.4 Hz, 1H, H-3″ or H-5″), 7.72 (d, *J* = 8.4 Hz, 1H, H-7), 7.91 (d, *J* = 3.9 Hz, 1H, H-3′) ppm. ^{13}C NMR (DMSO-d_6) δ 30.52 (β CH_2), 53.11 (αC), 118.92 (C7), 124.41 (C4′), 125.24 (C5″), 125.80 (C3″), 126.57 (C6), 127.33 (C2′), 128.10 (C4″), 130.18 (C4), 130.30 (C2), 130.45 (C3′), 132.41 (C5), 136.35 (C2″), 141.03 (C3a), 142.33 (C5′), 151.62 (C7a), 180.65 (CO_2H) ppm. MS (FAB) *m/z* (%): 372 ($[M+2H]^+$, 11), 371 ($[M+H]^+$, 32), 278 (19), 186 (70), 154 (100). HRMS: (FAB) *m/z* for $C_{18}H_{15}N_2O_3S_2$; calcd 371.0524, found 371.0522.
17. Berlman, B. In *Handbook of Fluorescence Spectra of Organic Molecules*, 2nd ed.; Academic Press: New York, 1971.
18. Guzow, K.; Szmigiel, D.; Wróblewski, D.; Milewska, M.; Karolczak, J.; Wiczk, W. *J. Photochem. Photobiol. A: Chem.* **2007**, *187*, 87–96.
19. (a) Becker, R. S.; Seixas de Melo, J.; Maçanita, A. L.; Elisei, F. *J. Phys. Chem.* **1996**, *100*, 18683–18695; (b) Seixas de Melo, J.; Silva, L. M.; Arnaut, L. G.; Becker, R. S. *J. Chem. Phys.* **1999**, *111*, 5427–5433; (c) Dufresne, S.; Bourgeaux, M.; Skene, W. G. *J. Mater. Chem.* **2007**, *17*, 1166–1177; (d) Seixas de Melo, J.; Burrows, H. D.; Svensson, M.; Andreson, M. R.; Monkman, A. P. *J. Chem. Phys.* **2003**, *118*, 1550–1556.